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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,094	08/04/2006	Nicholas S. Bodor	0056192-000001	1615

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EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,094	BODOR, NICHOLAS S.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,60 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/4/06 and 11/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-37, 60 and 61 are pending in the present application and examined herein on the merits for patentability. No claim is allowed at this time.

Specification

The disclosure is objected to because of the following informalities: the blanks identifying the provisional patent application numbers on page 25, lines 12 and 14 must be replaced with the application numbers. Appropriate correction is required.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 4 August 2006 and 8 November 2007 were filed before the mailing of a first Office action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of symptoms of L1210, hairy cell leukemia, chronic lymphocytic leukemia and Waldenström's macroglobulinaemia, does not reasonably provide enablement for treatment of symptoms of all leukemias. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention
2) the state of the prior art
3) the relative skill of those in the art
4) the predictability of the art
5) the breadth of the claims
6) the amount of direction or guidance provided
7) the presence or absence of working examples
8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The nature of the invention

The claimed invention relates to a method for the treatment of symptoms of multiple sclerosis, rheumatoid arthritis and leukemia in a subject suffering from said

symptoms comprising administering a saturated cladribine-cyclodextrin complex formulated into a solid oral dosage form.

The state of the prior art

As discussed in the instant specification, cladribine has been used to treat experimental leukemias such as L1210 and clinically for hairy cell leukemia and chronic lymphocytic leukemia as well as Waldenstrom's macroglobulinaemia. It has also been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions including rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) and multiple sclerosis (see e.g., J. Liliemark, Clin. Pharmacokinet, 32(2): 120-131, 1997).

Leukemia is a broad term covering a spectrum of diseases. Leukemia is clinically and pathologically subdivided into a variety of large groups. The first division is between its acute and chronic forms. Additionally, the diseases are subdivided according to which kind of blood cell is affected. This split divides leukemias into lymphoblastic or lymphocytic leukemias and myeloid or myelogenous leukemias. Finally, hairy cell leukemia and T-cell prolymphocytic leukemia are usually considered to be outside of this classification scheme.

The relative skill of those in the art

One of relative skill in the art is apprised of the various antileukemic drugs available and which drugs are suitable for which forms of leukemia. For instance, Chronic lymphocytic leukemia is probably incurable by present treatments, but the primary chemotherapeutic plan is combination chemotherapy with chlorambucil or

cyclophosphamide, plus a corticosteroid such as prednisone or prednisolone; many different anti-cancer drugs are effective for the treatment of acute myelogenous leukemia, and most oncologists rely on combinations of drugs for the initial, *induction phase* of chemotherapy; the standard of care for newly diagnosed patients with chronic myelogenous leukemia is imatinib therapy; and T-cell prolymphocytic leukemia is difficult to treat, and it does not respond to most available chemotherapeutic drugs.

The predictability of the art

The efficacy of any given drug for the treatment of all forms of leukemia is unpredictable. In fact, some forms of leukemia are difficult if not impossible to treat.

The amount of direction or guidance provided

The instant specification provides support for the treatment of L1210, hairy cell leukemia and chronic lymphocytic leukemia as well as Waldenstrom's macroglobulinaemia, but does not provide any direction or guidance with respect to the treatment of all leukemias.

The presence or absence of working examples

The instant specification provides phase solubility data and pharmacokinetic data for cladribine-cyclodextrin complexes, but does not provide any working examples of treating leukemia.

The quantity of experimentation necessary

It would require undue experimentation to determine if the compositions of the instant invention are efficacious against all forms of leukemia.

Therefore, for the aforementioned reasons, the Applicant is enabled for treatment of symptoms of L1210, hairy cell leukemia, chronic lymphocytic leukemia and Waldenström's macroglobulinaemia, but is not reasonably enabled for treatment of symptoms of all leukemias.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. It is noted that "substantially free of cyclodextrin in excess of the minimum amount required to..." is a term of degree. However, the instant specification defines "substantially free" as meaning 20% of the exact calculated amount. In the case of the expression "substantially free of cyclodextrin in excess of the minimum amount needed to maintain substantially all of the cladribine in the complex," the minimum amount of cyclodextrin needed to maintain the cladribine in the complex is obtained from phase solubility studies. On the other hand, when the expression "substantially free of cyclodextrin in excess of the minimum amount needed to maximize the amount of cladribine in the complex" is used, less than the aforenoted amount of cyclodextrin may be utilized and a larger amount of cladribine may be present in the dosage form in uncomplexed form as a result.

It is also noted that claims 8-11, 20-23 and 33-35 recite "about" or "approximate". The instant specification states that the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

2. Claims 11, 12, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is a relative term which renders the claim indefinite. The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The broadness of the term "a point located on a phase solubility diagram" does not necessarily render the term indefinite. However, no standard is given for what "phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is referred to in the claim, such as what temperature, pressure, or solvent this phase solubility diagram describes. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention from the term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-37, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US 6,194,395).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Schultz et al. teach oral solid dosage forms containing a mixture of cladribine and cyclodextrin (col. 1, ln. 4-10), suitable for the treatment of hairy cell leukemia, multiple sclerosis and rheumatoid arthritis (col. 6, ln. 42-49). The solid dosage forms contain from about 1 to about 15 mg of cladribine or its pharmaceutically acceptable salts, and from about 100 to about 500 mg of a cyclodextrin (col. 2, ln. 31-38); wherein any of the physiologically tolerable water-soluble substituted or unsubstituted cyclodextrin are suitable, such as α-, β-, and γ-cyclodextrin or derivatives thereof, with the most preferred cyclodextrin being hydroxypropyl-β-cyclodextrin (col. 2, ln. 54 through col. 4, ln. 33). Schultz et al. teach that cladribine is significantly more stable against hydrolysis when combined with cyclodextrins (col. 5, ln. 28-36). Schultz et al. further teach a greatly increased solubility of cladribine in water through use of the cyclodextrin

formulation, as shown in the phase solubility study (i.e., saturated cladribine-cyclodextrin formulations) (col. 7, Example 2, Table 2). See also claims 8-14.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Schultz et al. do not specifically teach the weight ratio of cladribine to cyclodextrin is from 1:35 to 1:50, such as 1:46 or 1:42, as instantly claimed. However, Schultz et al. teach that the solid dosage forms contain from about 1 to about 15 mg of cladribine or its pharmaceutically acceptable salts, and from about 100 to about 500 mg of a cyclodextrin (col. 2, ln. 31-38). Therefore, one of ordinary skill in the art would readily be able to optimize the weight ratio to achieve efficacious dosage forms.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

With regard to claim 37 and the method for enhancing bioavailability of cladribine from a solid oral or transmucosal dosage form, one of ordinary skill in the art would perform these steps in view of Schultz et al. Schultz et al. teach that uncomplexed cladribine normally undergoes hydrolysis in the acid pH of the stomach contents, but when complexed with cyclodextrin the stability is significantly enhanced (col. 5, ln. 28-36). Schultz et al. determined the solubility of cladribine in water at various concentrations of 2-hydroxypropyl-β-cyclodextrin (i.e., added excess cladribine and determined how much was soluble) (Example 2). Therefore, it would have been obvious for one of ordinary skill in the art to solubilize the maximum amount of cladribine in the cyclodextrin complex by adding excess cladribine (same as the solubility test according to Example 2), remove the excess uncomplexed cladribine that would normally undergo hydrolysis in the stomach, and concentrate the cladribine/cyclodextrin complex into a solid oral dosage form.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to prepare cladribine/cyclodextrin complexes wherein the maximum amount of cladribine is complexed with the cyclodextrin in order to increase solubility and stability to hydrolysis in the pH of the stomach, as reasonably taught by Schultz et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/Johann R. Richter/
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